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REACTIONS OF THE 2-HYDROXYTHIOPHENE
AND THE 2-HYDROXYFURAN SYSTEMS

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INAUGURAL DISSERTATION

by

ANNA-BRITTA HÖRNFELDT

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*By due permission of the faculty of science of the University
of Lund to be publicly discussed in lecture hall A of the Institute
of Chemistry, Helgonavägen 5, October 18, 1968 at 10¹⁵ a.m. for
the degree of doctor of philosophy. In addition to this survey
the papers numbered I—XI will be publicly discussed.*

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Tautomeric properties and some reactions of the 2-hydroxythiophene and the 2-hydroxyfuran systems^{1,2}

This thesis is a summary of the following publications:

- I. Hörnfeldt, A-B and Gronowitz, S, Unsaturated γ -thiolactones. III. Preparation and tautomeric structure of some methyl-, bromo- and methoxy substituted thiolenes-2-ones. *Arkiv Kemi* 21 (1963) 239.
- II. Hörnfeldt, A-B, Unsaturated γ -thiolactones. IV. Preparations, tautomeric structures and tautomeric equilibria of some 5-substituted thiolenes-2-ones. *Arkiv Kemi* 22 (1964) 211.
- III. Hörnfeldt, A-B, Unsaturated γ -thiolactones. V. On the rearrangement of some 5-alkyl substituted thiolenes-2-ones. *Acta Chem. Scand.* 21 (1967) 673.
- IV. Hörnfeldt, A-B, Unsaturated γ -thiolactones. VIII. A comparison of the rearrangement of the 5-methyl- and 5-tert.butylthiolenes-2-ones with the corresponding butenolides. *Arkiv Kemi* 29 (1968) 229.
- V. Hörnfeldt, A-B, Unsaturated γ -thiolactones. X. Tautomeric rearrangement of the 5-chloro- and 5-fluorothiolenes-2-ones. *Arkiv Kemi* 29 (1968) 427.
- VI. Hörnfeldt, A-B, Unsaturated γ -thiolactones. XI. Deuterium exchange in 5-methyl-4-thiolenes-2-one. *Arkiv Kemi* 29 (1968) 455.
- VII. Hörnfeldt, A-B, Unsaturated γ -thiolactones. XII. Tautomeric rearrangement of the 5-methylthiolenes-2-one system under the influence of various pyridine bases. *Arkiv Kemi* 29 (1968) 461.
- VIII. Hörnfeldt, A-B, Unsaturated γ -thiolactones. IX. Dissociation constants and UV-spectra of the 5-methyl- and 5-tert.butylthiolenes-2-ones. *Arkiv Kemi* 29 (1968) 247.
- IX. Hörnfeldt, A-B, Unsaturated γ -thiolactones. VI. The structure of some oxidative coupling products of 5-alkyl substituted thiolenes-2-ones. *Acta Chem. Scand.* 21 (1967) 1952.
- X. Hörnfeldt, A-B, Unsaturated γ -thiolactones. VII. Dimerisations of 5-alkyl substituted thiolenes-2-ones. *Arkiv Kemi* 28 (1968) 363.
- XI. Hörnfeldt, A-B, Dimerisation of 5-methylbutenolide. *Arkiv Kemi* 28 (1968) 571.

In the following discussion the papers will be referred to by the above Roman figures.

A series of derivatives of the 2-hydroxythiophene system, substituted with halogen, methoxy, aryl and alkyl groups, has been prepared. The tautomeric structures and the thermodynamic equilibria have been determined by means of NMR-spectroscopy.

The tautomerisation of 5-methyl- and 5-tert.butylthiolenes-2-one has been studied in methanolic solutions, pyridine serving as base. It was found that isomerisation was first-order with respect to both substrate and base, and that the base catalysis was general. A comparative reaction carried out with the oxygen analogue in benzene, using triethylamine as base, showed that the rate of rearrangement of the butenolides was 10^3 - 10^4 times higher than that of the thiolenes-2-ones. This observation is explained by d -orbital effects of the sulphur atom.

Since proton exchange is more rapid than isomerisation in both the 4-thiolenes-2-ones and the $\beta\gamma$ -butenolides, the degree of intramolecularity in the rearrangement process cannot be estimated. However, at least for the relatively acidic thiolenes-2-ones in methanol, which may be regarded as a dissociating medium, a two-stage intermolecular rearrangement mechanism is assumed, where a tridental anion is formed as an intermediate. This is also in agreement with the fact that the thiolenes-2-ones fulfil both parts of the Hughes-Ingold law.

In connection with the isomerisation experiments, the catalytic effect of various pyridine bases was examined. In the Brönsted diagram, the logarithms of the rates of the isomerisation catalyzed by the 4-substituted pyridines formed a straight line, whilst the values corresponding to the α -substituted compounds showed deviations which were a function of the steric circumstances.

In contrast to the butenolides, the thiolactones show enolic properties, and give acetates and, in certain cases, oxidative coupling products. Both systems undergo dimerisations of Michael type additions, in which the α -carbon as well as the γ -carbon of the tridental anion attack. Both systems undergo reactions characteristic for active methylene compounds giving condensation products. For most compounds prepared in the current investigation the IR-spectra are recorded and in some cases also the UV-spectra.

Introduction

The hydroxy, amino, and mercapto derivatives of benzene differ in many respects from the corresponding derivatives of the five-membered heterocycles with one hetero-atom. Thus whilst phenol, aniline, and thiophenol are simple, easily-available compounds of great importance as intermediates in benzene chemistry, the corresponding heterocycles have figured very sparsely in the chemical literature. In those cases where they have been mentioned, they have been described as very instable, this high reactivity is ascribed to their tautomeric properties (1, 2). In the benzene series, on the other hand, there is no supporting evidence for the occurrence of multiple tautomeric forms, even if very small proportions in equilibrium mixture cannot be entirely excluded (3).

2-Mercaptothiophene was isolated already in 1887 by Victor Meyer (4), but despite this, relatively little was known about the thiophene thiols until Gronowitz and co-workers instituted a series of NMR-investigations

of a number of substituted thiophene thiols in connection with the elucidation of the nature and mechanism of the thiol coupling. The structures of these compounds and of the amino-thiophenes were unravelled with the help of NMR-spectroscopy, and it was found that they existed exclusively in the amino and thiol forms (5, 6). This has also been shown later for the amino derivatives (6a).

It has long been known that the α - and β -angelica lactones are unsaturated γ -lactones (7, 8), whilst genuine 2-hydroxyfurans could not be demonstrated. True, the preparation of 2-hydroxyfuran has been described (9) but its enol structure has been questioned (10).

Even in the 2-hydroxypyrrole system, the oxo-form is assumed to be the thermodynamically more stable form, but the unsubstituted compound could not be prepared by reason of its great tendency to decomposition. Through introduction of methyl, phenyl, and carbethoxy substituents in different positions, more stable systems could be obtained which were shown by

¹ This paper is considered to be part XIII of the series of Unsaturated γ -thiolactones.

² Inaugural dissertation.

UV- and NMR-spectroscopy to be $\alpha\beta$ - and $\beta\gamma$ -unsaturated pyrrolones (11—15).

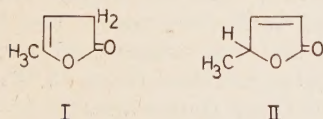
The 5-methyl-2-hydroxythiophene system was also prepared at the end of the 19th century (16), but all the attempts since the discovery of thiophene to synthesise the unsubstituted compound have failed, until in 1948 it was prepared by Hurd and Kreutz (17), who thus completed the series of simple thiophene derivatives. The structures of these compounds were elucidated by Gronowitz and Hoffman (18), who showed that they were unsaturated γ -thiolactones.

In the present investigation, the 2-hydroxythiophene system has been studied in greater detail, mainly with the help of NMR-spectroscopy. In the course of the work, it was found that the 2-hydroxythiophene system could advantageously be used as substrate in the study of the influence of the nature and positions of various substituents on the thermodynamic equilibrium.

The 5-alkyl-2-hydroxyfuran system and the 5-alkyl-2-hydroxythiophene system also proved to be suitable substrates for the study of the rearrangement mechanism of tautomeric systems.

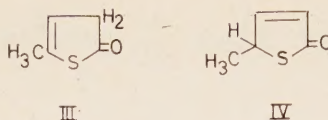
Methods of preparation

Already in the 1880s, 5-methyl- $\beta\gamma$ -butenolide, α -angelica lactone, I, was prepared through ring-closure of levulinic acid (7). Somewhat later, methods were developed for converting the non-conjugated form to the



conjugated one, β -angelica lactone, II (8). At about the same time, Kues and Paal obtained a product described by them as 5-methyl-2-hydroxythiophene through reaction between levulinic acid and phosphorous pentasulphide (16). This reaction was repeated in a modified form by Steinkopf and Thormann at the end of the 1930s (19). Their reaction product, however, had a higher boiling-point than the previously described product. These workers believed the earlier results to have been erroneously interpreted and assumed the product to have been 5-methyl-4-thiolen-2-one, III. After the NMR-studies by Gronowitz and Hoffman (18) of these compounds it is

thus plausible to assume that Kues and Paal obtained the lower-boiling $\beta\gamma$ -unsaturated form, III, through their more moderate method, whereas the

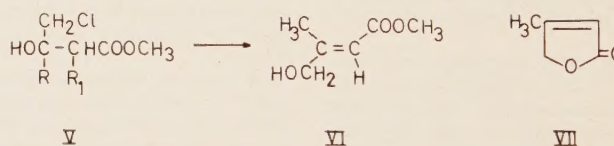


more drastic method of Steinkopf and Thormann yielded the thermodynamically more stable isomer, viz. the $\alpha\beta$ -unsaturated form, IV.

It is historically interesting to mention the ring-closure attempts of Mentzer and Billet (20) as well as the modified reaction in which 4-pentynoic acid was treated with phosphorous pentasulphide (21).

Butenolides

For the two hydroxy systems, the methods of preparation have devel-



In the current investigation a new method for the preparation of butenolides has been developed (IV). Furan and 2-methylfuran is treated with ethyllithium and the furyllithium thus obtained is converted with ethyl borate to the boronic acid ester, which is oxidised with 30 per cent hydrogen peroxide to the butenolide. From the 5-methyl substituted derivative, the $\beta\gamma$ -unsaturated form is mainly obtained, while the unsubstituted compound exists in the $\alpha\beta$ -unsaturated form. 5-Methyl- $\beta\gamma$ -butenolide was also prepared in the classical way by ring-closure of levulinic acid (7). 5-tert. Butyl- $\beta\gamma$ -butenolide was analogously obtained from β -pivaloylpropionic acid (IV).

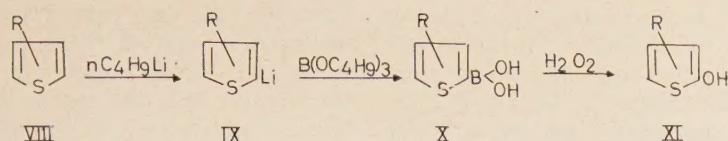
Unsaturated γ -thiolactones

In the case of the thiolactones, the new methods of preparation had thiophene derivatives as starting material. The main methods for preparation of phenols, the routes via diazonium salts or sulphonates, are inaccessible. The former due to the instability of the thiopheneamines and the later due to the drastic experimental conditions. It was found, however, that the milder methods for preparation of phenols

opened along different lines. In the case of the butenolides, work on the ring-closure method has continued and in a review by Rao from 1964 (22) many different methods are described. Most of these, however, have certain limitations, such as low yields, inefficient versatility, difficulties with respect to starting materials or problems in connection with working with polyfunctional compounds. Many of these difficulties are surmounted in the general method developed by Epstein and Sonntag for the preparation of $\alpha\beta$ -butenolides (23). The first step in all cases is the preparation of V via a Reformatsky reaction using α -chloro-carbonyl compounds as substrates. Compound V ($R = CH_3$, $R_1 = H$) gives when treated with base an epoxide intermediate, which isomerises to VI. Compound VI and related compounds were converted into the butenolides by photoirradiation in the presence of acid catalyst, VI gave VII.

could be used. Hurd and Kreuz (17) treated 2-thiophenemagnesium bromide with oxygen in the presence of isopropyl bromide and obtained a rather low yield of 2-thienol. Similar results were obtained by Hurd and Anderson (24) when they treated 2-thienyllithium with 1,2,3,4-tetrahydro-1-naphthylhydrogen peroxide. Despite the low yields, these methods were used in the preparation of the 5-phenyl-2-hydroxythiophene system (25).

During recent years, many hitherto unknown derivatives of the 2-hydroxythiophene system have been prepared. Thermal dealkylation of tertiary butyl ethers, developed by Lawesson and co-workers (26—28), proved to be a very useful method. The method used throughout in the current investigation (I, II, V, IX) is oxidation of boronic acid derivatives with hydrogen peroxide, a technique employed by Ainley and Challenger (29) and by Hawthorne (30) in the preparation of phenols. The boronic acids are obtained by reacting monosubstituted thiophenes or 2-bromothiophenes with butyllithium and treating the thienyllithium, IX, thus obtained with butyl borate. This preparative route is particularly appealing, since Gronowitz



and co-workers have developed a large number of methods for the preparation of substituted thienyllithium. These methods exploit both the aromatic character of thiophene and the sequential exchangeability of halogens with metal (31). Because of their tendencies to deboronise (32), the boronic acids were not isolated but were directly oxidised in ethereal solutions with hydrogen peroxide. In certain cases, when the tendency to deboronisation was exceptionally strong, the boronic acid esters were oxidised.

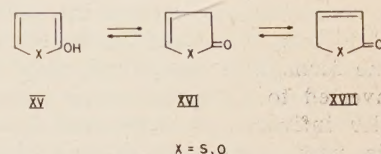
The only case causing real difficulties was the attempted preparation of 2-isopropylthiophene from thiophene. Most of the known methods for direct alkylation lead to isomer mixtures (33), and the attempted catalytic reduction of 2-propylidene

thiophene did not give complete hydrogenation. The best method proved to be reduction of 2-propylidene thiophene with sodium in ethanol (II), which gave a yield comparable to that obtained in a multi-stage cyclisation reaction (34).

Compared to the dealkylation method, the boronic acid method is more convenient, since thienyllithium is convertible with perbenzoate only in low yield, which means that the lithiumorganic derivative must first be converted to the corresponding Grignard reagent (26). The dealkylation method is advantageous when it is desired to introduce substituents which must be protected against the metal-organic compound. In those cases, the technique is to use the *tert*-butoxy group as a protected hydroxyl func-

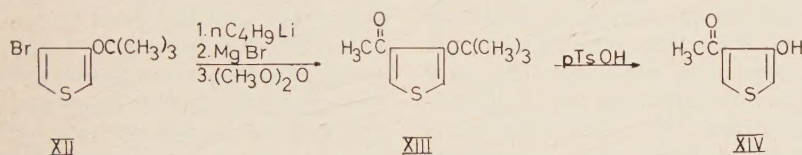
chemical methods are based on test-reactions, which are rapid in comparison with the rate at which the components are isomerising. Generally the chemical methods are not very satisfactory and were employed before their drawbacks were known. Much more realistic values are obtained by the physical methods especially by the spectroscopic ones.

For both the 2-hydroxythiophene and the 2-hydroxyfuran systems, three tautomeric forms exist. Besides the enol form, XV, two lactone forms are



conceivable. The non-conjugated $\beta\gamma$ -unsaturated form, XVI, will be designated as 4-thiolen-2-one ($X = \text{S}$) or $\beta\gamma$ -butenolide ($X = \text{O}$), whilst the conjugated $\alpha\beta$ -unsaturated form, XVII, will be analogously designated as 3-thiolen-2-one or $\alpha\beta$ -butenolide, as the case may be. In all the tautomeric forms of the 3-, 4- or 5-substituted compounds, only three hydrogen atoms participate in the tautomeric system. Consequently, NMR-spectroscopy has been of unprecedented usefulness in structure determination and in establishing the proportions of the different tautomeric forms. The NMR-spectra of 3-substituted thiolen-2-ones (I) exhibit two bands with relative intensities of 1:2 for the ring-protons, thus excluding the enol form as well as the non-conjugated form.

The effect of the substituent in the 3-substituted thiolen-2-ones on the 4-hydrogen is governed by the substituent's inductive and mesomeric effects. Methoxy and methyl groups cause shifts towards higher field, and bromine towards lower field (I), in analogy with the shifts of the *cis*-hydrogens in substituted ethylenes (44, 45) and propylenes (46, 47). In contrast to the situation prevailing in the thiophenes (48) and furans (49), the $-I$ -effect of bromine in these compounds seems to dominate over its $+M$ -effect, a circumstance which is reflected by the shift of the 4-hydrogen towards lower field. If the effect of the shift of the 3-hydrogen in thiophenes substituted in the 2-position with bromine, methyl or methoxy is compared with that of the 4-hydrogen in the corresponding 3-substituted 3-thiolen-2-ones, it is seen that the effect



tion, XII, whereafter the other functional groups are introduced. In this way, Lawesson and co-workers prepared a large number of carbonyl-containing hydroxy thiophenes (35, 36). Certain carbonyl-containing compounds have also been synthesised by the boronic acid method (37, 38) or by ring-closure reactions developed by Fiesselmann and co-workers (39, 40). In principle, this last synthesis consists of a reaction between methyl this glycolate and acetylene derivatives, β -ketoesters or $\alpha\beta$ -dihalo-carboxylates, the resulting adduct then being cyclised in a Dieckmann reaction.

Since the 2-hydroxythiophene system tautomerises easily under the influence of acids and bases, or on warming (II), the dealkylation method easily gives the thermodynamically most stable form. In most cases, however, the thermodynamically less stable form may be obtained by dissolving the tautomeric mixture in alkali and acidifying the common anion thus obtained (II). In the case of the chloro and fluoro substituted compounds, however, it was found that the anion was not sufficiently stable for this procedure (5). Since the boronic acid method is so mild, it was always possible to isolate a product which con-

sisted largely of the 4-thiolen-2-one form. In the case of the chloro derivative, the dealkylation method gave mainly the more stable $\alpha\beta$ -unsaturated form (41). Of the 5-halogen substituted compounds, the bromo derivative seems to be the most reactive (cf. p. 11).

3,5-Dinitro-2-hydroxythiophene and 3-nitro-5-acetyl-2-hydroxythiophene were obtained from nitrochlorothiophenes by causing them to react with sodium formate in methanol (42). These compounds are colourless crystalline substances which decompose with evolution of oxides of nitrogen and give rise to dark-coloured tars even at -20°C .

Buch and Köbrich (43) have recently shown that when nitrobenzene is treated with two moles of phenyllithium at -100°C , almost two moles of phenol are obtained. This may possibly be a plausible synthetic route even in the thiophene series.

NMR-spectra and tautomeric structure

Various methods are available for the determination of tautomeric structures. These methods can be divided into physical and chemical ones. The

in the case of the thiolactones ($\Delta\tau = 1.40$ ppm) is greater than in the case of the thiophenes ($\Delta\tau = 0.89$ ppm) (50). This difference may depend on the fact that in the latter compounds the mesomeric charge-displacement is spread over the whole aromatic system whereas in the former compounds it is confined to the 4-position.

In the case of the 5-alkyl substituted compounds it was possible to isolate two forms (II). Oxidation of 5-alkyl-2-thiophene boronic acids with hydrogen peroxide gave principally one isomer whose NMR-spectrum showed two ring-hydrogen bands of intensities 1:2, proving it to have the 4-thiolene-2-one form. This compound could be converted to a higher-boiling isomer under influence of acids and bases. This new compound showed three absorption bands of equal intensities in its NMR-spectrum, indicating it to have either the enol form or the 3-thiolene-2-one form. The two bands which lie in the region of the thiophene hydrogen absorptions are split into quartets with a common coupling constant of 5.9–6.3 c/s. This excludes the enol form, since J_{34} in true thiophenes is 3.45–4.35 c/s (51). The values of the shifts and coupling constants of the 5-alkyl substituted derivatives measured in acetone solutions show that both parameters for the ring-protons fall within well-defined intervals which, in the case of the shift values, do not overlap one another even if one goes from one tautomeric form to the other. The 4-hydrogen in the conjugated form absorbs at the lowest field (2.50–2.70 τ), after which comes the band belonging to the second ethylenic hydrogen in the conjugated form at 3.70–3.80 τ . The ethylenic hydrogen of the non-conjugated form absorbs in the interval 4.45–4.60 τ . About 1 ppm upfield, at 5.50–5.75 τ , comes the absorption of the 5-hydrogen in the conjugated form, and at the highest field falls the absorption band of the CH_2 -group in the 4-thiolene-2-ones. That the respective absorptions of the ethylenic hydrogens in the 3-thiolene-2-ones were assigned correctly is supported by the shifts (2.05–3.40 τ) of the 4-hydrogens in the 3-substituted derivatives. True, the shifts of the 3- and 4-substituted derivatives were measured in cyclohexane solutions, but by comparing the τ -values measured for both of the 5-methylthiolene-2-ones in cyclohexane and acetone, it is apparent that the τ -values found in cyclohexane are in-

variable higher, the discrepancy being at the most 0.30 ppm (I). It is interesting to note the large down-field shift of the 5-hydrogen in the 5-halo substituted compounds, which is about 2 ppm lower compared to the 5-hydrogen in the 5-alkyl substituted compounds (V).

In the case of both the unsubstituted and the 4-substituted compounds it was possible to isolate only one tautomeric form, which had absorption bands of relative intensities 1:1:2 and 1:2 respectively in the NMR-spectra, excluding in both cases the enol form. If the substituent effect is taken into account, and the shifts of these compounds are compared with those of the previously mentioned substances, it is clear that the previously made assumption that both the unsubstituted (18) and the 4-substituted compounds (I) exist in the conjugated form are correct.

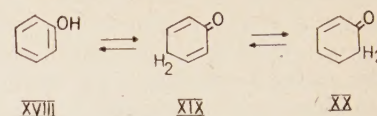
In all the above-mentioned thiolene-2-ones, the ring-hydrogens give rise to first-order spectra, in which even some side-chain couplings could be obtained. Especially interesting is the large long-range coupling (52) over five bond-distances in the 5-alkyl-4-thiolene-2-ones (II). This coupling is considerably larger for 5-methyl-4-thiolene-2-one (2.6 c/s) than for 3-methyl-3-thiolene-2-one (1.9 c/s) (I), possibly because the carbonyl group in the latter compound causes the methyl group to be somewhat displaced out of the plane of the ring. In 5-ethyl- and 5-*n*-propyl-3-thiolene-2-one (II), the coupling of the 5-hydrogens to the α -hydrogens in the side-chain have different magnitudes. This discrepancy may be ascribable to the fact that the 5-hydrogen is localized at an asymmetric carbon (53, 54).

The NMR-spectra of the butenolides were of the same type as those of the thiolactones. The shifts of the ring-protons in both forms fall within the same interval as those for the 5-alkyl substituted thiolactones. The coupling constants for the ethylenic hydrogens are equally large in both systems, whilst $J_{4-\text{CH}_2}$, J_{35} and J_{45} are somewhat smaller in the butenolides than in the thiolactones (IV).

Structure and thermodynamic stability

As mentioned above the instability and high reactivity of the butenolides and thiolactones are ascribable to their tautomeric properties (1, 2).

However, the fact that these heterocycles can exist in three tautomeric forms, XV–XVII, ought not in itself account for the differences from the benzene derivative, XVIII, since even



this could conceivably exist also in the two keto forms, XIX and XX. Calculations of the binding energies for $-\text{CH}-\text{C}=\text{O}$ and $-\text{C}=\text{C}-\text{OH}$ show in addition that the keto structure is more stable than the enol one by 18 kcal (55). However, the hypothetical cyclohexadienone form of phenol would be accompanied by a loss of about 35 kcal mole⁻¹ in resonance energy, hence the enol form is the energetically preferred one. Conant and Kistiakowsky (56) have calculated the free energy for the enolisation of cyclohexadienone to be -18.6 kcal mole⁻¹. Of the three forms, XV–XVII, the enol form is the most aromatic one, and since aromaticity decreases in the series thiophene, pyrrole and furan, the enol form should be most favoured in the thiophene system. Very varying values for the resonance energies of thiophene and furan are given in the literature, however, some of them are rather low, 20 (56a) and 17 (62) kcal mole⁻¹ respectively. These energies are comparable with the energy stabilizing the keto structure over the enol structure. By utilizing this low values for the resonance energies the fact that many of the 2-hydroxythiophene and 2-hydroxyfuran systems exist as lactones becomes more understandable.

In the tautomeric system characteristic for 2-hydroxythiophene and 2-hydroxyfuran, four carbon atoms and one oxygen atom participate, which makes these systems pentade ones. However, since the compounds studied in the present investigation could only very rarely be demonstrated directly to exist in the enol form, these systems may be regarded as triade systems of carbon-carbon tautomerism and the carbonyl group comprises the activating group.

About 40 years ago, Kon, Linstead and co-workers (57) carried out an extensive investigation of open triade systems based on butene derivatives such as XXI and XXII. The investigation was made possible by reason of Linstead's method of analysing mix-

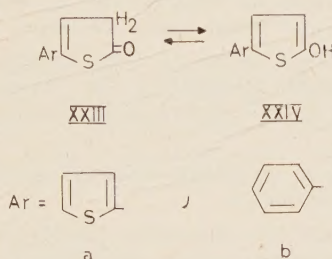


ture of $\alpha\beta$ - and $\beta\gamma$ -unsaturated isomers through exploiting the different rates with which they reacted with bromine (58). Equilibration was generally catalysed by strong alkali, which is too drastic for all the determinations to be fully reliable. The results have later been discussed by Baker and Ingold and were considered in relation to the conjugation and hyperconjugation effects (59, 60). The availability of the more reactive thiolactones, which can be studied under milder conditions and by spectroscopic methods, was taken as an incentive to new experimental work on the carbon-carbon tautomerism.

NMR-spectroscopy makes it possible to determine the proportions of the various components in a mixture, and comprises a very useful tool for studying how the thermodynamic equilibrium between the $\alpha\beta$ - and $\beta\gamma$ -unsaturated forms in the thiolen-2-one system is affected by the nature of the different substituents and by their positions in the molecule. Unsubstituted thiolen-2-one exists mainly as 3-thiolen-2-one (18) since conjugation of the double-bond with the carbonyl group contributes to the free energy of this form; such an increment in the free energy is excluded in the $\beta\gamma$ -unsaturated form, since here the double-bond is isolated. A substituent in the 3-position conjugates and hyperconjugates with the $\alpha\beta$ -double-bond, an effect which co-operates with the carbonyl's conjugation with the double-bond. In the 4-substituted compounds, the substituent conjugates and hyperconjugates with the $\alpha\beta$ - as well as with the $\beta\gamma$ -double-bond. This is a secondary effect, but the $\alpha\beta$ -form is favoured by reason of the extended conjugation with the carbonyl group. In the 3- and 4-bromo, 3- and 4-methyl and 3-methoxy substituted thiolen-2-ones, it was only possible to demonstrate the occurrence of the 3-thiolen-2-one form (I), in accordance with the above reasoning.

In 5-phenyl- and 5-thienyl-thiolen-2-one (II), the increment in resonance energy obtained when the aryl substituent conjugates with the $\beta\gamma$ -double-bond ought to be of the same order of magnitude as in vinyl benzene, viz. ca 7 kcal mole⁻¹ (61). This resonance energy is considerably larger than the difference in the resonance energies

of 2-butene and crotonaldehyde ($\Delta E = 2.2$ kcal mole⁻¹) (62), which is a measure of the energy gain resulting from the conjugation of the carbonyl group with the double-bond. In the 5-aryl substituted thiolen-2-one system, the conjugation in the $\alpha\beta$ -unsaturated form between the $\alpha\beta$ -double-bond and the carbonyl group is over compensated by the conjugation of the 5-substituent with the $\beta\gamma$ -double-bond, and the thermodynamically more stable form is thus the $\beta\gamma$ -unsaturated lactone, XXIII. This is also borne out by



the NMR-spectrum, in which the ring-hydrogen resonances have intensities of 2:1. In methanol solutions, however, the 4-thiolen-2-one is in equilibrium with a new component whose shift and coupling constants are in agreement with those of 5-phenyl- and 5-thienyl-2-methoxythiophene (II). This new component comprises 25–30 per cent of the mixture and may be ascribed to the enol form, XXIVa, which is presumably stabilised in the methanol solution partly through extended conjugation and partly by association with the solvent.

In the 5-alkyl substituted thiolen-2-ones as well as in the butenolides, the conjugation energies in the $\alpha\beta$ -forms are compensated to a certain extent by the hyperconjugation of the 5-substituent with the double-bond in the $\beta\gamma$ -unsaturated form, thus endowing both forms with comparable energies. Introduction of methyl, ethyl, *n*-propyl, *n*-butyl, isopropyl or *tert*-butyl groups in the 5-position enables both tautomeric forms to be isolated in each system. These rearrange to an equilibrium mixture of 3-thiolen-2-one and 4-thiolen-2-one in the presence of catalytic amounts of acids and bases. Measurements show that the proportions of the $\beta\gamma$ -form in the equilibrium diminishes as the hydro-

gens of the methyl group are successively exchanged for methyl groups in the series methyl, ethyl, isopropyl and *tert*-butyl, whilst unsubstituted 3-thiolen-2-one exists mainly in the $\alpha\beta$ -unsaturated form (cf. Table 3 in (II)).

Hyperconjugation, however, does not seem to be the only effect responsible for the stabilisation of the $\beta\gamma$ -unsaturated form, since its proportion in the equilibrium mixture is more or less independent of the length of the *n*-alkyl chain, with the exception of ethyl.

If, however, electron-attracting groups are introduced, both the 2- and the 3-hydroxythiophenes exist mainly as enols. In the case of the 2-hydroxyfuran system the keto form seems to be somewhat more favoured (63). This may be a function of the extra stabilisation due to extended conjugation between the $-M$ and $+M$ substituents. The reason for enol structures of the aldehyde, carboxyl and carbethoxy substituted compounds (35–38) can also be intramolecular hydrogen-bonding. Even the 5-carbonyl-3-hydroxy compounds exist as enols, which is also the case with 5-phenyl-3-hydroxythiophene (25). However, the influence of the hydrogen-bonding cannot be determined by the method employed.

It might generally be said that electron-attracting groups tend to stabilise the enol form. Hurd and Kreuz (42) do not discuss the tautomeric structure of the nitro substituted compounds they studied, but even these should reasonably exist as enols.

When the functional group is located at the β -position in the thiophene or furan, the number of possible tautomers is reduced to two, viz. XXV and XXVI. Katritzky has sug-



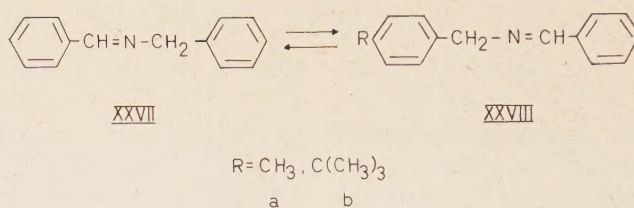
gested that since in the 2-substituted isomers there exists a crossed conjugation, which does not occur in the 3-substituted isomers, the aromatic enol form should be more favoured in the case of the former than in the case of the latter isomer (64). However, the results of the experiments carried out to date show that the reverse condition actually prevails. Introduction of a methyl group at the 2-position of the 3-hydroxythiophene system results in a dominance of the enol form over the

keto form (4:1). Changes in the substituents at the α -position is accompanied by changes in the keto-enol ratios, which is in agreement with the hyperconjugation effects the substituents are expected to exert (65). Unsubstituted 3-hydroxythiophene has been described by Ford and Mackay (1), who from considerations of IR-data consider it to exist in both the enol and keto forms. The compound, however, is extremely unstable, which has also been confirmed by later experiments (35, 66).

Kinetic measurements

In order to gain an insight into the detailed mechanism of the tautomerisation of the 2-hydroxythiophene and 2-hydroxyfuran systems, it was of interest to study the tautomerisations kinetically. Two different mechanisms have been suggested in the earlier literature, a two-stage unimolecular mechanism (67) and a single-stage bimolecular one (68).

The two-stage mechanism was described by Ingold, Shoppee and Thorpe, who assume a free mesomeric anion which has a finite, independent existence. In connection with this mechanism, Ingold and Hughes made the following generalisation: "When a proton is supplied by acids to the mesomeric anion of weakly ionising tautomers of markedly unequal stability, then the tautomer which is the most quickly formed is the thermodynamically least stable: it is also the tautomer from which the proton is lost most quickly to bases." (69). This generalisation is especially applicable when the unsaturated carbanion is stabilised through charge-displacement to the electronegative components, as in the phenylnitromethane system, which is a classical example of a tautomeric system (70). Even the diphenylpropene system and its nitrogen analogue, viz. the azomethines or the aza-allylic systems, have been of great interest (71–75). Some of the results of studies of these systems seem to favour the single-stage mechanism (76, 77). Even if de Salas and Wilson (78) question the results, the single-stage mechanism remained an alternative in the discussions (79, 80) right up to 1965, when Cram and Guthrie (81, 82) showed that it was not sufficiently well-grounded and that under certain conditions some aza-allylic systems follow the Hughes-Ingold law, since the ambident anion reacts more quickly at that side which



gives the thermodynamically more stable tautomer (79, 83). In recent years it has been demonstrated that, parallel to the intermolecular mechanism, there exists a competing mechanism which under certain conditions becomes the dominating one. In this mechanism, the proton displacement is intramolecular and contains ion-pairs as intermediates. Pioneers in this field are Bergson and co-workers (84) and Cram and co-workers (85), who in a series of experiments have elegantly established the intramolecular nature of these tautomerisations.

NMR as an analytical tool in kinetic measurements

Since the absorption bands of the ring-protons and the side-chain hydrogens had different τ -values in the two tautomeric forms in both the 2-hydroxythiophene and 2-hydroxyfuran system, certain absorption resonances could be used as analytical bands. The absorptions of the 4-hydrogen in the non-conjugated form and of the 5-hydrogen in the conjugated form proved to be a good combination, and absorption due to the side-chain was also a useful band. Which of the possible combinations was the best depended on other factors, such as the solvent and catalyst used. The thiolactones were preferably studied in methanol with pyridines as catalyst, under which conditions the aliphatic part of the NMR-spectrum could be profitably employed, even in those cases where the pyridine was alkyl substituted. In the kinetic experiments with the butenolides where triethylamine served as base, the aromatic absorptions were used as analytical bands. This was also the case for the thiolactone system when acetone was used as solvent.

The solvent and base chosen were such as to give first-order kinetic rates with half-lives suitable for this type of NMR-determination (cf. Figs and Tables in IV), which do not differ from other classical methods of analyses. Since the thiolactone system is very reactive, the choice of experimental conditions is rather limited.

Both the butenolides and the thiolactones undergo nucleophilic ring-opening in the presence of strong bases. When amines serve as base, they should be tertiary ones to avoid reaction with the carbonyl group.

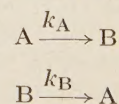
The tautomerisation was followed by noting the increase in intensity of the analytical absorption band of the component formed, and the decrease in intensity of the band due to the component consumed. The intensities were determined through integration, and here employment of the side-chain (methyl and tert.butyl) absorptions as analytical bands offers greater accuracy, since these are three times and nine times more intensive, respectively, than the ring-proton bands. In the runs performed, the sums of the integrals of the increasing and decreasing bands were constant within the accuracy limits of the apparatus, which shows that no side-reactions had taken place during the time the reaction kinetics were studied.

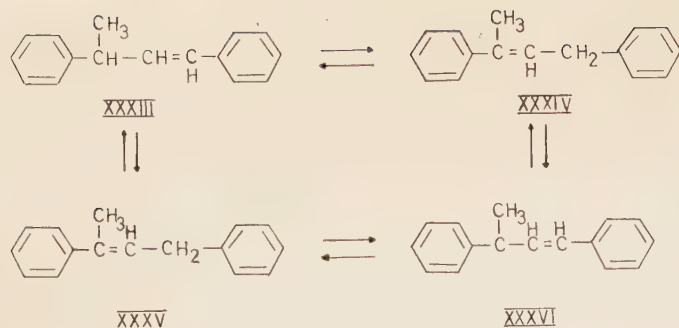
In the current investigation, the kinetics of primarily 5-methyl- and 5-tert.butylthiolene-2-one together with those of the corresponding butenolides were studied (III, IV). In all the determinations, an equilibrium between the two tautomeric forms was established which depended not only on the external conditions but also on the nature of the substituent. In the case of the 5-fluoro- and 5-chlorothiolene-2-one, the equilibrium position was displaced entirely in favour of the conjugated form (V). The conditions used and the equilibrium constants are collected in Table 1.

The results in all the isomerisation experiments satisfied function (1)

$$\ln \frac{AK - B}{A_0K - B_0} = -(k_A + k_B)t \quad (1)$$

which shows that the two opposing reactions are of first-order and can be described in principle as follows:





on the other hand, incorporation of deuterium during the time required for isomerisation is negligible, a fact which indicates that tautomerisation is intramolecular under these conditions. In the extensive investigation by Cram and co-workers on the base-catalysed rearrangement proceeding via a carbanion intermediate of compounds XXXIII—XXXVI, it was found that these systems undergo proton-deuterium exchange much more rapidly than isomerisation (94). Through comparisons with similar systems, these authors assumed that half of the proton transfer proceeds intramolecularly. Since the unsaturated carbanion in the butenolide system is stabilised through charge-displacement to the carbonyl group, it is highly probable that the rearrangement in these systems follows both parts of the Hughes-Ingold law, which is not irreconcilable with a two-stage mechanism. Thus the butenolides and indenones isomerise at comparable rates under similar conditions, though different tautomerisation mechanisms may be operating.

Deuterium-exchange in 5-methyl-4-thiolen-2-one

A feature in the elucidation of the tautomerisation mechanism of the 5-methylthiolen-2-one system was the measurement of hydrogen-exchange. In recent times, a number of papers dealing with the relative rates of enolisation at two positions in simple unsymmetric ketones have been published (95, 96). The enolisation process has been studied through following hydrogen-exchange by means of the NMR-technique (97, 98). In these ex-

periments, relatively low rates were recorded, in spite of the quite drastic conditions.

A qualitative experiment showed that in the thiolactones, hydrogen-exchange at the 3-position of the non-conjugated form occurs much more rapidly than rearrangement, whilst the acidic 5-hydrogen of the conjugated form exchanges at a rate comparable with the isomerisation rate. By working with very low pyridine concentrations in deuteromethanol it was possible to follow kinetically exchange of the 3-hydrogen in 5-methyl-4-thiolen-2-one (VI). A comparison with ethyl acetoacetate, whose keto form has a pK_a -value (99) comparable to that of nitromethane (100) and a few units higher than that of the non-conjugated thiolactone, shows that hydrogen-exchange in 5-methyl-4-thiolen-2-one occurs more rapidly than in the ethyl acetoacetate, and much more rapidly than in nitromethane. In the comparison it was assumed that the rates were equal to two and three times k_{obs} , respectively (101, 102). The difference, however, is of the order of magnitude concurrent with the relation between the kinetic and thermodynamic acidities of similar systems (103). This implies that the thiolactones are pseudoacids of the ethyl acetoacetate type.

Mechanism of tautomerisation

The reaction mixture used in the kinetic experiments contained besides solvent, thiolactones, and their common anion, also two other acid-base pairs, namely pyridine-pyridinium ion in equilibrium with methanol-methoxy ion. In paper III it was shown that

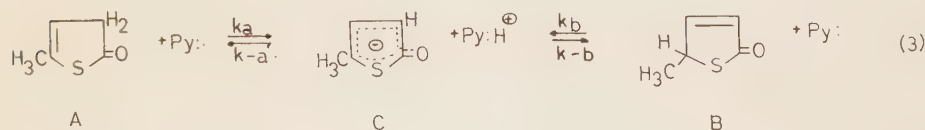
isomerisation was proportional to base concentration, and that the straight line obtained by plotting isomerisation rate against base concentration passed through the origin. From the linearity one may conclude that the methoxide ion's contribution to the catalysis cannot be large, by reason of its low concentration. Also, since the line passes through the origin, catalysis by the solvent can be neglected. In connection with experiments dealing with the dependence of the isomerisation on the structure of the base, it was found that the tautomerisation was general base catalysed (105, 106). In the Brønsted diagram, the logarithms of the rates catalysed by 4-substituted pyridines formed a straight line, whilst the values corresponding to the α -substituted pyridines exhibited deviations which were a function of their steric requirements (VII).

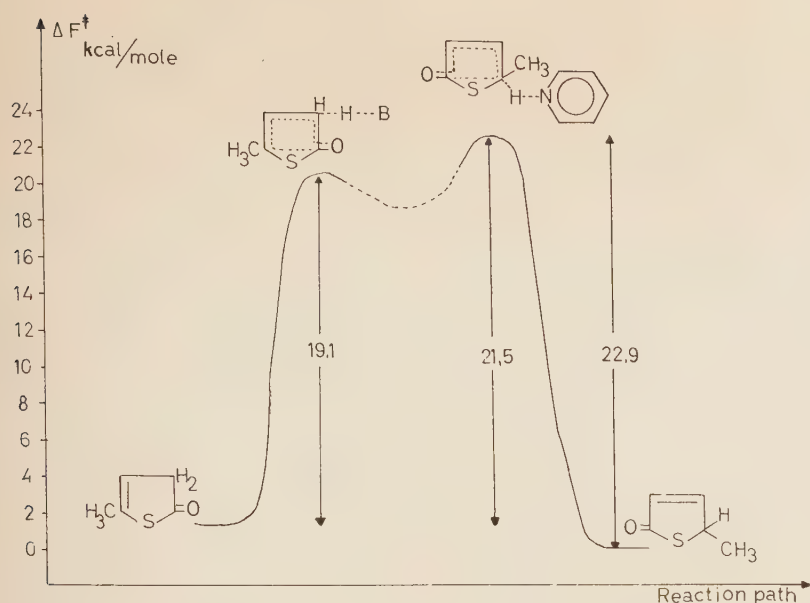
With the information obtained from the study of the carbon-carbon tautomerism of the 2-hydroxythiophene system, one can, following Cram's nomenclature (107), set up the following schematic representation of the pyridine-catalysed tautomerisation in methanol at 18° C (see below).

The thermodynamic equilibrium constant, which is determined by the quotients of the specific rate-constants for A and B ($K = k_A/k_B$), is equal to 10.6. Furthermore, the collapse quotient $k_{-a}/k_{-b} \gg 1$, since acidification of the common anion gives principally the thermodynamically less stable $\beta\gamma$ -unsaturated form, A. The 5-methylthiolen-2-one system fulfils even the second part of the Hughes-Ingold law, since the 4-thiolen-2-one form also loses protons to bases faster than the 3-thiolen-2-one form, B. The value of k_a was obtained from the hydrogen-exchange experiments. In compounds of the same degree of acidity as A ($pK_a = 8.29$) (cf. p. 10), it is always the removal of the proton which is the slow step (108, 109), whilst the rate-constant for addition of proton, k_{-a} , can be calculated from relation (4).

$$k_a/k_{-a} = K_{acid} \quad (4)$$

The exact value of k_{-a} cannot be determined from our data, since the dissociation constant for 5-methyl-4-thiolen-2-one has been measured in aqueous solutions, whilst k_a is the rate at which the 3-hydrogen exchanges with deuterium in deuteromethanol. Though the rate of hydrogen-exchange was measured at very





low base concentrations, it could be calculated for the same base concentration as was used in the isomerisation experiments from the base dependence, and k_a/k_b could be approximately estimated to have a value of 835 (VI).

Since both hydrogen-exchange and isomerisation have been studied at different temperatures, the activation parameters have also been determined (see Table 3). The profile of free activation-energy versus reaction co-ordinate which is described by reaction (3) is depicted in the scheme above. The free energy values are taken from Table 3.

The diagram is of classical type and is in agreement with both parts of the Hughes-Ingold law. Since hydrogen-exchange is more rapid than isomerisation, nothing can be said about the degree of intramolecularity (94). However, considering the degree of acidity of the system, it is quite conceivable that at least in such a highly dissociating medium as methanol tautomerisation should proceed principally intermolecularly by way of a free anion (110, 111). That the 5-position is involved in the rate-determining step is also supported by the dependence of the activation entropies on the nature of the 5-substituent. Thus when methyl was exchanged by tert.butyl, the ac-

tivation entropy decreased by 6 cal mole⁻¹ degree⁻¹ (III). The requirement of the microscopic reversibility also presupposes that the pyridine-pyridinium ion pair is responsible for both removal and addition of the proton in the 5-position, which constitutes the rate-determining step in the isomerisation.

Other physical data

IR-spectra

From the IR-spectra it is possible to draw certain conclusions about the tautomeric structures of both the 2-hydroxyfuran and 2-hydroxythiophene systems. None of the compounds of these systems exhibits a convincing OH-stretching band, neither in the solid nor in the liquid states. On the other hand, they show strong carbonyl absorptions. In contrast to the butenolides, however, the thiolactones can react as enols and give derivatives of the hydroxy form (I, II, V, IX), which means that at least small hitherto non-demonstrable amounts might occur in the equilibrium mixture.

The carbonyl absorptions of the 5-alkyl-4-thiolen-2-ones lie in an interval, which is well separated from the region where the 5-alkyl-3-thiolen-2-ones have their carbonyl absorptions (II). Even at lower frequencies there

are well-defined absorption intervals characteristic for each of these two thiolactone forms. In the 5-chloro and 5-fluoro substituted derivatives, the carbonyl stretching frequencies still occur within different intervals in the two tautomeric forms, though the bands are displaced towards each other (V).

The 3- and 4-substituted thiolen-2-ones, which can be isolated only in the thermodynamically most stable conjugated form, have also their carbonyl absorption bands in the interval as the 5-substituted 3-thiolen-2-ones (I).

An examination of the corresponding bromo compounds reveals that the carbonyl stretching frequency for 3-bromo-3-thiolen-2-one is higher than that of 4-bromo-3-thiolen-2-one. This shift, which is caused by the α -halogen, is a well-known effect in carbonyl compounds and has been extensively studied by Woodward (112), Djerassi and Scholz (113) and especially by Jones and co-workers (114—116).

In connection with studies on the fine structure of the carbonyl absorption and keto-lactol tautomerism in esters, the IR-spectra of a large number of lactones have been examined (117, 118). The data thus obtained together with those derived from the four butenolides studied in the current investigation show that the carbonyl stretching frequencies for the $\alpha\beta$ - and $\beta\gamma$ -unsaturated forms occur at different intervals in these compounds, both of which lie at higher frequencies than those of the thiolactones (IV).

UV-spectra

UV-spectroscopy has proved to be very useful in the study of tautomeric structures and determination of compositions of equilibrium mixtures. The structures of amino and hydroxy substituted pyridines and pyrimidines have been elucidated with its help (119), as well as problems of ring-chain tautomerism in β -benzoylacrylic acid (120) and in benzoylbenzoic acids (121). In order to establish the wavelengths and intensities of the absorption bands of the different tautomers, the UV-spectra of such derivatives which could be expected on theoretical ground to have the same spectrum as the corresponding tautomer were examined. This method is a rather qualitative one. If it is desired to estimate small amounts of one tautomeric form in an equilibrium

Table 3. Rates, enthalpies, free energies and entropies of activation for the isomerisation and deuterium exchange of 5-methylthiolen-2-one in methanol catalysed by pyridine at 18°C (table 2 in Paper VI)

Reaction	Base conc. (mole l ⁻¹)	$k \cdot 10^3$ (min ⁻¹)	$\Delta H^\ddagger$ (kcal mole ⁻¹)	$\Delta F^\ddagger$ (kcal mole ⁻¹)	$\Delta S^\ddagger$ (cal mole ⁻¹ degree ⁻¹)
Deuterium exchange	0.001	23	7.0	21.6	—50.1
Deuterium exchange	0.2	1835	7.0	19.1	—41.4
Isomerisation A $\rightarrow$ B	0.2	25.3	10.9	21.5	—36.5
Isomerisation B $\rightarrow$ A	0.2	2.2	12.5	22.9	—35.9

mixture, the dissociation constants of such methyl derivatives are determined, where both the one and the other tautomeric structures are locked (122, 123).

This technique has also proved to be useful in investigations of cyclic azolinethiones which are in equilibrium with corresponding mercapto compounds. The equilibrium constants are of the order 10^6 – 10^8 in favour of the thione form (124).

In the case of the thiolen-2-one system, it was thus possible to prepare ethers which give the same type of UV-spectrum as the enol form. In the case of the two keto forms, however, it is more difficult to prepare suitable derivatives.

3-Thiolen-2-one gives in ethanol solutions one band at $220\text{ m}\mu$ and one at $265\text{ m}\mu$. In analogy with the butenolides (125), Hurd and Kreuz (17) assumed that the band at $220\text{ m}\mu$ was characteristic for the $\alpha\beta$ -unsaturated form. They did not discuss the band at $265\text{ m}\mu$, which was ascribed by Kosak and co-workers to the thiolactone structure (25). This band appears at longer wavelengths than the UV-band of 2-methoxythiophene. For 5-phenyl-2-thienol, such a shift relative to the absorption of the corresponding ether could not be observed (25).

Introduction of substituents in the 3- and 4-position renders the band at $220\text{ m}\mu$ substituent-dependent and causes it to be displaced towards lower frequencies by methyl, bromo and methoxy groups, whilst the $265\text{ m}\mu$ band is not affected by the substituent (I).

The alkyl substituted compounds have a strong band at $220\text{ m}\mu$, which has not been more closely investigated to date. The bands for 3-thiolen-2-ones at $265\text{ m}\mu$ and for 4-thiolen-2-ones at $268\text{ m}\mu$, however, have been studied in greater detail (II). The intensities of these bands are substituent-dependent. For the $\beta\gamma$ -unsaturated γ -thiolactones the band intensity increases with the length of the side-chain when going from methyl to *n*-butyl, the difference in $\log \epsilon$ being 0.22. For the 3-thiolen-2-ones, the difference in $\log \epsilon$ is only 0.11 and there is no correlation between the length of the side-chain and the extinction coefficient, which is consistently larger for the conjugated form than for the $\beta\gamma$ -unsaturated one, a circumstance most conspicuous in the case of the methyl derivative.

Only little is known about the UV-

data of the $\alpha\beta$ - and $\beta\gamma$ -unsaturated butenolides. Most of the spectra were recorded in connection with the location of the double-bonds in more complex compounds, for example, in pseudosantonin (125, 126). The results so obtained showed that the conjugated compounds have a strong maximum in the region of 210 – $224\text{ m}\mu$ whilst the $\beta\gamma$ -isomers only show weak absorption. This is not in agreement with the UV-spectra of the 5-methyl- and 5-tert.butyl-butenolides. Both tautomeric forms have a strong band at 212 – $219\text{ m}\mu$, and the difference in the $\log \epsilon$ value is 0.40 in favour of the conjugated form (VIII). Thus in the region of the UV-absorptions, the butenolides have one and the thiolactones have two absorption bands: how they are correlated to each other is not convincingly clear from the MO-calculations made for both of these analogous systems (cf. p. 11).

Dissociation constants

In connection with the kinetic measurements, it was of interest to determine the dissociation constants for both systems. The thiolactones had such degrees of acidities that the methods used for phenols could also be applied to them. Both potentiometric titration and UV-spectroscopy showed that the CH-acidity of the thiolactones was of the same order of magnitude as the OH-acidity of phenols (VIII). Since both of these methods of determination necessitate work in alkaline environment, they cannot be applied to the butenolides since they undergo facile nucleophilic ring-opening (127). However, they seem to be less acidic than the thiolactones, since they isomerise very slowly (IV) — slower even than 1-methylindene (93) (for indene $\text{p}K_a = 21$). Since the butenolides are carbonyl compounds, their dissociation constants cannot be determined by the method for estimation of acidities introduced by Conant and co-workers (128) and developed by Mc Even (129) and Streitwieser and co-workers (130), which is based on competitive metalation.

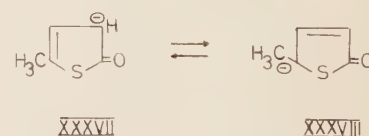
Dipole-moment

The composition of the equilibrium mixture has been examined in different connections, including in conjunction with kinetic measurements in various solvents (III, IV, V) and in measurements of dissociation constants to enable the individual $\text{p}K_a$ -values to be determined for the apparent dissociation constants (VIII).

In both cases the previous observation has been verified that the composition of the equilibrium mixture is dependent on the polarity of the solvent. In the series cyclohexane, acetone and nitromethane, whose dipole-moments are 0, 2.80 and 3.5 D the dominance of the $\alpha\beta$ -form increases (cf. Table 3 in paper II). From this it may be deduced that 3-thiolen-2-one is more polar than 4-thiolen-2-one. The butenolides behave in a similar manner: if one goes from benzene to pyridine, the equilibrium constants for both 5-methyl- and 5-tert.butyl substituted butenolides increase (IV). The dipole-moments were recorded in cyclohexane solutions: for 5-methyl- and 5-tert.butyl-3-thiolen-2-one a value of 4.4 D was obtained, whilst the values for the corresponding 4-thiolen-2-ones were 3.7 D and 3.8 D respectively. The agreement with the calculated values is discussed below.

MO-calculations

Since Hückel's LCAO procedure for molecular orbital calculations has shown itself to be adaptable to the calculation of diverse physical properties, calculations on both of the thiolen-2-ones and on both butenolides have been made by the ω -method, modified by Janssen and Sandström (131). The result shows that the π -electron density is greater in the 3-position than in the 5-position of the ambident anion (XXXVII, XXXVIII),



where the two values are 1.247 and 1.158 respectively. This is in agreement with the postulate that the thermodynamically less stable isomer is formed first when an alkaline solution of the 5-substituted thiolactone is acidified (II). The total π -electron energy for the thiolactone forms is also in accord with experience. Thus the $\alpha\beta$ -unsaturated form, which is the more stable, has a total π -electron energy of 4.06β , whilst the less stable $\beta\gamma$ -unsaturated form has a value of 3.98β . If, however, the calculated values are correlated with the UV-measurements, the agreement is less good. The two bands in the spectra of the thiolactones may legitimately be ascribed to excitations to both of the antibonding orbitals, and this assumption is verified in the case of the $\beta\gamma$ -

unsaturated form. For the $\alpha\beta$ -unsaturated form, on the other hand, the observed shift between the two bands is smaller than predicted. When comparing the butenolides with the thiolactones, one would expect, by reason of the greater possibility for conjugation in the sulphur containing system, lower energy for the first $\pi-\pi^*$ transition, and consequently the absorption maximum in the thiolactones should show a bathochromic shift in comparison with that of the oxygen analogue. The calculations, however, do not give differences large enough to account for the observed shift (VIII), it is more likely that the band at 220 $m\mu$ should answer for the same transition, but such an assumption makes it very difficult to account for the band at 270 $m\mu$ of the thiolene-2-one, since it is far too intense to be ascribable to an $n-\pi^*$ transition (132).

The large discrepancies between the calculated and experimentally found values may depend on the fact that when the molecular orbital method, which was actually worked out for acyclic systems, was applied to these small rings, the electronic repulsions were not taken sufficiently into account.

Better agreement between the calculated and found values is obtained in the treatment of the dipole-moments. The π -moment calculated by the ω -technique was found to be 1.9175 D for the non-conjugated form and 2.9987 D for the conjugated one. Since the geometry of both forms is so similar, their σ -moment may be regarded as comparable, hence the difference in the π -moments should be made up of the difference in the total dipole-moment. The experimentally determined difference was 0.6–0.7 D, and the deviation from the calculated value is what could be expected, since the ω -method neglects interaction between the σ - and π -moments (133).

Some reactions of thiolene-2-ones and butenolides

Phenolic reactions

The enol forms of neither the butenolides and the thiolene-2-ones could not be detected by spectroscopic methods, with the exception of the two 5-aryl substituted thiolene-2-ones (cf. p. 5). Despite this, however, esters could be prepared from bromo and alkyl substituted thiolactones (I, II, V, IX), which exhibit in their NMR-spectra ring-proton shifts and cou-

pling-constants characteristic for disubstituted thiophene derivatives (32). 3-Methyl- and 3-methoxy-thiolene-2-one could not be converted to the pure acetate neither by treating the starting material with excess of acetyl chloride or by Schotten-Baumann acylation method (I). Unlike the benzoates the acetates appear to be so easily hydrolysed that they were always contaminated with starting material. Bromo substituted acetates could be prepared in a pure state, but they decomposed after a while.

In connection with this it is interesting to note that the NMR-spectra of 5-alkyl-2-acetoxythiophene showed hard coupling of the 3- and 4-hydrogens, and the low-field region exhibited structures ascribable to side-chain couplings (II). These coupling-constants had the same order of magnitude as J_{CH_3-3} in some 2-methyl-5-alkyl substituted thiophenes (134), which indicates that the 4-hydrogen resonance lies at lowest field, which in turn would imply that the alkyl group is somewhat less electron-donating than the acetoxy group.

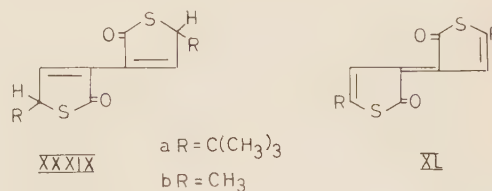
Ethers have been prepared from 5-phenyl- and 5-thienyl-4-thiolene-2-one through reaction with dimethyl sulphate (II). Both of these ethers ex-

hibit characteristic thiophene data with respect to shifts and coupling constants. In the former case, the NMR-spectrum shows an additional methyl band which indicates that, besides O-alkylation, even C-alkylation had occurred, though which of the three carbon atoms had reacted has not yet been examined in detail (II).

The butenolides, on the other hand, cannot be converted to the corresponding acetoxyfurans (135), nor do they show other enolic reactions.

The thiolene-2-ones did not give the characteristic ferric chloride reactions of enols and phenols. Ferric chloride seems to have only oxidising effect and gives products of indigoidal structure (19). These are also very easily obtained on contact with air, the alkyl substituted compounds giving rise to red-coloured products and the aryl substituted compounds to blue ones (II).

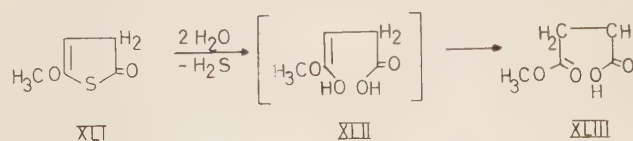
In the preparation of 5-tert.butyl-4-thiolene-2-one, an oxidative coupling product was isolated as a by-product (IX). Since the NMR-spectra of both the by-product and its acetate were exceptionally simple, the compound is very probably symmetrical. Furthermore, since ortho coupling is more probable than meta coupling, the com-



pound is assumed to have structure XXXIXa. This was convincingly verified by the authentic synthesis of the compound (IX). In the case of the methyl substituted product, XXXIXb, a coupling of 7.40 c/s was found, which shows that one of the hydrogen is localised geminal to the methyl group. A number of attempts were made to prepare dithiolene-2-ones through oxidation of the monomer. However, positive results were only obtained when potassium ferricyanide or chloranil were used as oxidising agents, though oxidation went too far and the indigoidal product, XLa, was isolated (IX).

Products of type, XL, could also be obtainable through decomposition of the reactive 5-bromo-thiolene-2-one. Jakobsen showed that from 5-bromo-3-thiolene-2-one, the reduced 3-thiolene-2-one and a product having only one absorption band in the NMR-spectrum are formed (41).

The 5-methoxy-thiolene-2-one system proved also to be very reactive. The only identifiable product that could be isolated (in its attempted synthesis) was monomethyl succinate (XLIII) which indicates that the 4-thiolene-2-one (XLI) that is first formed undergoes ring-opening with loss of sulphur (II).



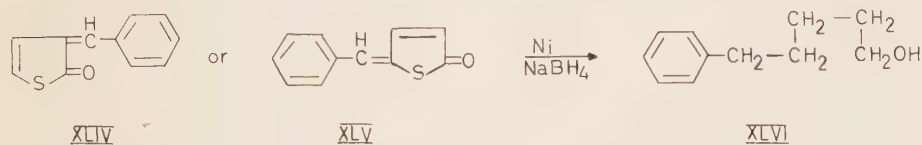
The reactivity of the thiolene-2-one system is also demonstrated in that these derivatives are in some cases attacked by solvents. When 5-methylthiolene-2-one was treated with hydrogen chloride in methanol, the neutral products that could be isolated comprise of 5-methyl-2-methoxythiophene and methyl levulinate (II). In the presence of base in alcoholic solutions, both the butenolides and the thiolactones undergo nucleophilic ring-opening.

Reaction at the active methylene group

Already in one of the first studies on the butenolides, they were condensed with benzaldehyde and anisaldehyde under the influence of amines (8). In the various thiolene-2-ones, the active methylene group was con-

densed with benzaldehyde and piperonal in acid-catalysed reactions (I, II, V). Piperonal was chosen in the case of the 5-alkyl substituted compounds in order that crystalline derivatives may be obtained in the whole series (II). Acid-catalysed condensation in the case of 3-methoxy-3-thiolene-2-one was unsuccessful, the failure depending on the fact that the compound, as an enol ether, is especially sensitive to acids (II). Neither did base-catalysed condensation give any results, though it was used successfully by Oettingen in the case of butenolides (136) and by Plieninger and Decker in their work on pyrrolones (11).

Both unsubstituted as well as 4-substituted thiolene-2-ones can give rise to two condensation products, depending on whether the compound reacts as the 4- or as the 3-thiolene-2-one. These condensation products



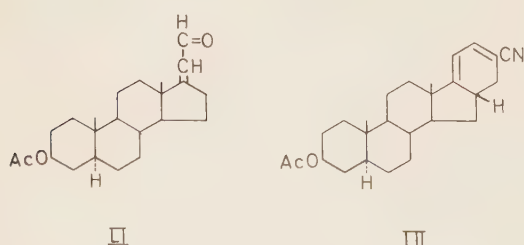
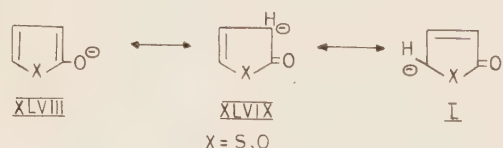
(XLIV or XLV) could be converted to 5-phenyl-pentanol-1, XLVI, through desulphurisation with Raney-nickel and treatment with sodium borohydride, which shows that condensation occurs at the 5-position (I).

The 3- and 4-bromo substituted condensation products have very different melting points (137–138° C and 76–77° C respectively) (II), which may be related to *cis-trans* isomerism of the benzylidene hydrogens, a structural detail which may possibly be elucidated by means of NMR-spectroscopy. An other compound interesting from the NMR point of view is 3-acetonilidene-5-methyl-4-thiolene-2-one, XLVII, where couplings from the methyl group in the 5-position to the acetone

methyl groups could be recorded (II). Coupling over as many as seven bond-distances have hitherto been known only in polyacetylenic compounds (52, 137).

Michael addition type dimerisations

Both thiolactones and butenolides have properties characteristic for compounds participating in Michael reactions. When treated with base, they give a trident anion which may be regarded as a resonance hybrid of



the formal structures, XLVIII–L. In addition the conjugated form is a typical acceptor. Earlier, unsubstituted thiolene-2-one has been used as acceptor in reactions with conventional active methylene compounds as donors (138).

Generally, when an ambident anion serves as donor, attack occurs at the carbon that is α to the carbonyl group (139), which in these cases would give 3-adducts. In the condensation of dypnone, an other pentad system, an intermediate of γ -addition type was assumed. Other workers, however, thought it improbable that dypnone's methyl hydrogens are so reactive that it should serve as donor, and suggested an alternative mechanism (140).

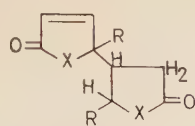
A more convincing example of γ -attack is the γ -cyanoethylation of the aldehyde, 3 β -acetoxy-5 α -pregna-17-en-21-al, LI, which after aldol cyclisation gives 3 β -acetoxy-16 α -ethyl-16 β -cyano-16 β ,21-cyclo-5 α -pregna-17,21-diene, LII (141).

In the formation of Michael adducts from thiolactones and butenolides, however, the γ -carbon seems to be the most reactive giving LIII, and the frequency of occurrence of 3-adducts, LIV, is a function of the magnitude of the substituent on the 5-carbon (X, XI). Besides this position-isomerism, the possibility also exists for tautomerism and diastereomerism. In the dimerisation of unsubstituted 3-thiolene-2-one, two tautomeric forms of the 5-adduct were observed. When the substituent at the 5-position was methyl, both 3- and 5-adducts were isolated, and when it was *tert*.butyl, two diastereomers of the 3-adduct were obtained (X).

It seems to be a general rule that the unsaturated ring of the dimer has the same structure as the most stable form of the monomer. A further example of this is the dimer isolated by Jakobsen and Lawesson from the 3-carbethoxy-2-hydroxythiophene system (30). In this case the most stable form is the enol one, imparting the thiophene structure to the unsaturated ring.

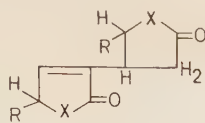
Two diastereomeric 5-adducts from 5-methylbutenolide were known earlier (135, 142), but since the thiolactones also gave 3-adducts, the dimer mixture obtained from 5-methylbutenolide was re-examined. The NMR-spectrum of the crude product indicated that one 3-adduct, LIV, and two 5-adducts, LIII, were present. By means of column-chromatography, the

3-adduct could be separated from the two 5-adducts. These two 5-adducts could also be separated from each other by suitable choice of solvent combinations (XI).

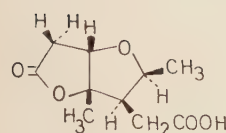


LIV

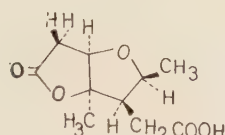
X = S, O

R = CH₃, C(CH₃)₃

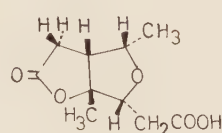
LV



LVI

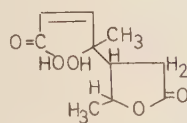


LVII



LVIII

different conditions. In both cases, the respective workers had treated the dimers with alkali and subsequently acidified the solutions, whereby they obtained acids of different melting points. The acids were assumed to be diastereomers of LV. These experi-



LV

ments were repeated because the dimers themselves had very similar melting points. Hydrolysis, however, gave in both cases products whose NMR-spectra did not exhibit absorptions, except for those belonging to the carboxyl group, lower than at 5.90 τ and 5.58 τ , excluding any type of ethylenic hydrogens (143). Neither did the esters of these acids show OH-absorptions in their IR-spectra. Structure, LV, may consequently be regarded as incorrect, hence structures LVI—LVIII have been suggested as alternatives (XI). In the construction of these structures, certain restrictions were imposed, namely, that the internal Michael reaction proceeds via a trans addition and that the rings are *cis*-annulated. This is supported by the fact that when the 3-adduct is hydrolysed, it is reformed on acidification as the thermodynamically most stable product.

The Vilsmeier formulation of 5-methyl-thiolene-2-one (144) is an example of a substitution reaction. Even in this case introduction of an elec-

tron-attacking group favours the enol form. The evidence is not very convincing as these authors' assumption regarding the structure of the 5-methyl-2-hydroxythiophene system is incorrect.

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